forms the central turn in the toxin molecule starting within β-strand 7 and connecting it, via β-strand 8, to α-helix 4 (see Fig. 2). In SEB, this domain encompasses amino acids 150-161 (SEQ. ID NO.: 12). Such isolated peptides directly inhibit pyrogenic toxin-mediated induction of IL-2, INF-γ and/or TNF-β gene expression in normal peripheral blood mononuclear cells (PMBC). The expression of these genes is exquisitely sensitive to toxin (e.g., SEB) mediated activation. Likewise, antibodies against the peptides of the invention also bind to the toxins and can inhibit the expression of these genes, induced by any of SEB, a related toxin, SEA and a more distantly related toxin TSST-1, all of which can induce toxic shock in an individual.

REJECTIONS UNDER 35 USC §112, ¶2

Claims 50-84 have been rejected under 35 USC §112, ¶2 as indefinite. The Examiner has objected to the term "derivatives" in the claims as rendering the claims ambiguous.

Contrary to the Examiner's assertion, in the present case, the term "derivative" is well-defined in the specification as to the claimed peptides, and those of skill in the art would be readily able to ascertain the metes and bounds of the claims as required by Section 112, ¶2.

For example, the specification clearly and succinctly defines the term "derivatives" as meaning "peptides with any insertions, deletions, substitutions and modifications that are capable of eliciting protective immunity against toxic shock . . . ." *See* page 19, lines 14-18 and Claims 52-64. The specification provides numerous

examples of such modifications. For example, modifications may include a constrained conformation which "can be attained by internal bridges, short-range cyclizations, extensions or other chemical modification." *See* page 23, lines 13-14 and Claim 55 and 56. Modifications may also include dimerization or trimerization or multimerization. *See* page 23, lines 10-12 and Claims 52-54. The skilled artisan would be able to determine what is meant by the term "derivative" looking to the specification and the claims of the instant application. In fact, there are issued patents whose peptide-related claims include the term "derivative" that have equivalent or even less teaching in the specification compared to the present application, indicating that the United States Patent and Trademark Office considers this use of the term "derivative" as non-ambiguous (*i.e.* definite). *See, e.g.*, U.S. Patent No. 5,731,155 of Schreiber et al..

In addition, Claims 50, 52-64 and 76-84 have been rejected under 35 USC §112, ¶2 as indefinite. The Examiner has objected to the lack of a defined specific peptide sequence in the claims. The Examiner contends that the specific amino acid sequence must be recited so that one can compare the homology of the claimed peptide to the amino acid sequence of a domain of a pyrogenic exotoxin in order to determine the meets and bounds of the invention.

Applicants assert that the claims provide sufficient definition of the peptides by requiring that the purified and isolated peptides correspond to a particular defined region/domain of pyrogenic toxins that forms the "central turn" of such molecules indicates the meets and bounds of the invention. In addition, the claimed

peptides must be substantially homologous to this region/domain. Similarly, U.S. Patent No. 5,942,491 of Root-Bernstein also claims a peptide comprising an amino acid sequence which is homologous to residues of myelin basic protein. In addition, U.S. Patent No. 5,731,155 claims a peptide which "contains an amino acid sequence derived from a receptor for a cytokine." These patents clearly indicate that the United States Patent and Trademark Office does not require that the specific amino acid sequence be recited in the claims to determine the metes and bounds of the invention. In fact, if the sequence is required, a recitation of the homology requirement in the claims would be meaningless.

In addition, Claims 50, 52-64 and 76-84 have been rejected under 35 USC §112, ¶2 as indefinite. The Examiner has objected to the use of the phrase "connecting it" in Claim 50. Applicants have amended Claim 50 to indicate that the β-strand 7 is connected, via short β-strand 8, to α-helix 4. The amendment to Claim 50 adds no new matter. In addition, Claim 50 has been amended to correct a typographical error in the term"antagonizing."

In view of the remarks herein, Applicants maintain that those of skill in the art would be able to readily ascertain the metes and bounds of the claims, thereby obviating the §112, ¶2 rejection.

REJECTIONS UNDER 35 USC § 102(b)

Claims 50-84 stand rejected under 35 USC § 102(e) as allegedly anticipated U.S. Patent No. 5,705,151 of Dow et al ("Dow et al."). The Examiner

contends that Dow et al. teach a peptide (Dow et al. SEQ ID NO:2) which is 99.8% identical to the claimed amino acid sequence of SEQ ID NO:12 and which is capable of antagonizing toxin-mediated activation of T lymphocytes. In addition, the Examiner contends that Dow et al. teach a peptide (Dow et al. SEQ ID NO:2) that is substantially homologous to any one of peptides of SEQ ID NO:1-12. Applicants maintain that Dow et al. do not anticipate the claims of the present invention.

Applicants believe that the Examiner has misinterpreted Dow et al. which only discloses full-length toxin proteins. Moreover, Applicants assert, that while Dow et al. disclose a full length superantigen (*e.g.* SEB; Dow et al. SEQ ID NO:2) which is capable antagonizing toxin-mediated activation of T lymphocytes, Dow et al. fail to teach that a portion of the full length superantigen is capable of antagonizing toxin-mediated activation of T lymphocytes as claimed. The present invention, in contrast, teaches that a portion of an exotoxin (superantigen), *i.e.* a peptide that is not involved in binding of the toxin to the T-cell receptor or to MHC class II molecules, but forms the central turn in the toxin molecule starting with β-strand 7 and connecting the β-strand 7, via β-strand 8, to α-helix 4, is capable of antagonizing toxin-mediated activation of T lymphocytes. The skilled artisan, looking to Dow et al., would not be able to determine which portion of the full length superantigen has the capability of antagonizing toxin-mediated activation of T lymphocytes.

Similarly, Claims 50-84 stand rejected under 35 USC § 102(b) as allegedly anticipated by Tseng et al., Infect. Immun. 63(8): 2880-85(1995) ("Tseng et

al."). Applicants maintain that Claim 50-84 are also not anticipated by Tseng et al..

As indicated above, Claim 50 is directed to an isolated and purified peptide whose amino acid sequence is substantially homologous to a domain of the pyrogenic toxins that forms a central turn in the molecule starting with β-strand 7 and connecting β-strand 7, via β- Strand 8, to α-helix 4 (See Fig. 2 and Example 2). Claim 51 provides an isolated and purified peptide substantially homologous to the amino acid sequence of SEB in this domain (amino acids 150-161 of SEB). Claims 52-65 define various derivatives of the isolated peptide (e.g., dimerized and multimerized forms, conformationally stabilized forms and peptides having – and C- terminal additions) and specific sequences thereof, while the remaining claims define compositions comprising the isolated peptides. Thus, the present invention is directed to isolated peptides that are derived from, but do not constitute a full length toxin protein.

On the other hand, Tseng et al. teach administration of a SEB toxoid (a full length protein, not a peptide) in microspheres to monkeys in order to elicit neutralizing antibodies to SEB (toxin). Those monkeys that produced such antibodies to the toxoid appeared to survive a subsequent aerosol challenge with SEB. But, Tseng et al. neither teach nor suggest that the toxoid itself antagonizes SEB activity on cell.

It is well known that a toxoid is a chemically-modified full length toxin protein that retains the antigenicity (immunogenicity), but not the toxicity of a toxin protein. Thus, immunization with a toxoid can lead to production of an immune response to a toxin that, in some circumstances, is protective. For example, this is the basis for

immunization against diphtheria and tetanus.

In Tseng et al., SEB toxin (full length protein) had been treated with formalin and then alum precipitated to produce the toxoid used for immunization. The full length protein (in both Tseng et al. and Dow et al.) comprises the region that binds to the T-cell receptor or to MHC class II molecules as indicated in Tseng et al. page 2884 in the first full paragraph.

Tseng et al. specifically state that it is the SEB-class II complexes (that can only form if SEB contains the class II binding region) which activate T cells which then undergo apoptosis (*i.e.* they lyse) and it is the depletion (apoptosis) of these activated T cells in the mouse that results in anergy or a tolerant state. *See* Tseng et al. at page 2884, first full paragraph. Therefore, the skilled artisan could not determine from Tseng et al. or Dow et al. that a peptide that does not contain the region of the full length protein which binds to the T-cell receptor or to MHC class II molecules would still retain the capability of antagonizing (i.e., inhibiting) toxin-mediated T-cell activation.

In addition, neither Tseng et al. nor Dow et al. ever isolated any peptides corresponding to a particular domain of SEB as in the present invention, nor tested the ability of such isolated peptides themselves to inhibit SEB and other toxin (e.g., SEA, TSST-1) - mediated activities, such as activation of IL-2, IFN-γ and TNF-β gene expression, nor produced antibodies to the specific peptide that also inhibit toxin-mediated T cell activation, as in the present invention.

Furthermore, as documented in the present specification (*see, e.g.,* page 5,

lines 4-10; page 31, lines 1-5; page 43, lines through page 45, line 19 and page 51, lines 10-16), the ability to elicit antibodies to SEB by administration of toxoid, as shown in Tseng et al. is not predictive of whether such antibodies will antagonize (i.e., inhibit) toxin-mediated T-cell activation, nor inhibit toxin-mediated gene expression, as in the present invention. In fact, in some cases, antibodies to certain portions or domains of SEB actually potentiated toxin activity.

Moreover, there are issued patents which clearly indicate that a disclosure of a full length protein having a particular activity does not anticipate peptides derived from the full length protein which retain that activity. For example U.S. Patent No. 5,942,491 claims peptides derived from full length myelin basic protein which are capable of treating arthritis even though the prior art taught that full length myelin basic protein is capable of suppressing arthritis. In addition, U.S. Patent No. 5,731,155 claims peptides derived from a known receptor or cytokine which are capable of binding to transcription factors even though it was known in the art that the full length receptors and cytokines are capable of binding to transcription factors. Therefore, the United States Patent and Trademark Office does not consider that references teaching the activity of full length proteins are anticipatory of inventions teaching peptides derived from the full length proteins having the same activity.

For a reference to anticipate a claim under 35 USC § 102(b), the reference must teach each and every limitation of the claim. Scripps Clinic & Research Fdn. v. Genentech, Inc., 18 U.S.P.Q. 2d 1001, 1010-1011 (Fed. Cir. 1991).

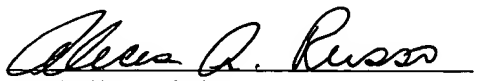
Tseng et al. and Dow et al. clearly do not teach each and every element of the invention as claimed, which is required for a rejection under Section 102, thereby obviating this rejection. Applicants request reconsideration and withdrawal of the rejections under 35 USC § 102.

Moreover, Tseng et al. and Dow et al. do not even suggest the presently claimed invention. There is clearly no suggestion whatsoever in these references of the claimed isolated peptides and compositions comprising them.

Conclusion

In view of the amendments to the claims and the remarks herein, Applicants maintain that Claims 50-84 are now in condition for allowance. A Notice of Allowance is earnestly solicited.

Respectfully submitted,



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